Learning about Learning A Course on Neurobiology of Learning and Memory
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Lecture – 01
Introduction to Learning and Memory - I: Historical perspective

Hello and welcome to the lecture 1 of the Learning about Learning lecture series, in this NPTEL course. And, in the as I was talking to you in the introductory lecture or the introductory brief video, we will be learning a lot about learning itself, the phenomena of learning, how it is existing or came into existence in organisms. And how we can study it, what we can understand from how we learn and how those learned information is stored in the brain. This notion of learning interested many people, interest you and me and it is in it interested very many people.

And one of the first to actually study and propose any mechanisms and to study this learning in a systematic manner dates back to German psychologists called Hermann Ebbinghaus. He argued, if learning were to happen one of the prominent manifestation of that would be our ability to store the learned information. So, we should be able to see or experience this learned information in terms of what the storage of this information we call it as memory. And, he wanted to study, that that is Hermann Ebbinghaus.

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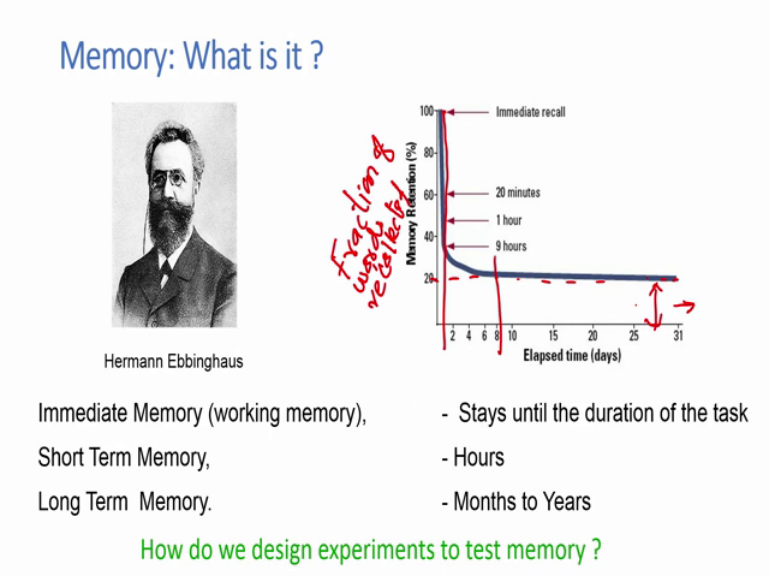

And how did he decide to study it? He decided to study it through experiments on him himself, it is called introspective experimentation. And, what he would do is that he would make word lists, word lists pretty much like if you are actually preparing for any competitive exam. So, where you would want to remember many many many things and these are new things then what you do is you make small cards, like small chits where you write a cheat what you call it as cheat codes where you write what the new information is, what the new word is either the meaning of it, how you use it or a definition of it and so on and so forth. Pretty much like that he would, he wanted to make a list of words.

However, he was very much aware of the fact if I am going to start and test memory then I need to start with a clean slate. What do I mean by clean slate? A brain which does not have a previous any information related to this that I am actually going to try to learn and store ok. If I want to put it in a perspective so, if I want I am going to learn about a cat and ask how well I remember what I have learned then its that much more helpful. And in fact, I want to make sure that I do not have any information about the cat before if I do have then it is going to bias what I am learning about the cat.

So, how would you start with a clean slate then, because as in adults lesson with many humans when we are doing the experiments this can be very hard. So, the way is did that is that he ensured the information that he is going to learn is new; even though he had lot many more related information like any adult (Refer Time: 04:01) And, that to us psychologist definitely he has a lot more information that he has acquired all his life, but what he can do is he can zero in on the informations that are not familiar to him before.

So, what he would do is that he would make something called as a triad. These are 3 letter words, he would choose the triad such as such that they follow a particular format. We call them as CVC triads Consonant Vowel Consonant triads. These are rare not to say that, they will not be there at all in any language, but they are rare in general. So, an example would be dax he c a t cat itself. So, like that he would form a three letter words long list of them and then he will go ahead and strike out those dictionary words. Dictionary words are those words that pre exists before like for example, cat I told you bat, pot all of them he would actually strike them out and then leave only those words that does not exist in the dictionary.

And in fact, he was so careful he would even go ahead and strike out any word that has resemblance to a dictionary word thereby he shortlisted about a 1000 or so triads. I mean write them in as sheet of paper put them all in a basket, pick one at a time and read out aloud with a monotonous voice without any modulation. The idea here this I am going to read this word, memorize it try to memorize it or in the here what you are doing is you are trying to acquire that memory are learning about that word learning the word not about that, but just the word. Then he will ask how many of these words in the word list in the list of words that I have decided to that I had picked up today right the in this experiment.

So, there is a basket in that there are lot of chits with these triads, I am picking one after the other and then each time I am reading it aloud. I now made a list that I have picked out today, later at later point in time he would actually come back and then say how many of those words that I picked out I am able to remember. So, that is the first kind of a question that you would like to ask right because, the idea of learning requires that you need to be able to store information that you have learned. The idea of storage tells you that you would be able to retrieve those information later in time, that is how you can test how well you are actually able to remember.

So, if what he did was he went ahead and plotted this remembrance fraction of the words that he was able to retrieve from that list as a function of time, the fraction of the words would relate back to remembrance. When he did that what he got was this wonderful little graph which is known as the forgetting curve. So, what he has plotted here is that memory retention as a percentage; essentially what he is doing here is he is measuring the fraction of the words that he was able to recollect, fraction of words recollected as a function of elapsed time. This is the time that is elapsed between when here and initially pulled out these words from the basket to the time at which point I, to the time of testing when actually he is testing it ok.

So, from this what he was from the graph what he was able to see is that there are words that are lost very quickly, very very quickly right like within a day or so, you are actually losing them. The there are some that are lost over a period of time, but that there is a constant fraction right, remember this is non-zero. There is about 20 percent of them that you never forget at all. So, set of words that you lose just then and there, a set of words that you lose gradually and the set or fraction about 20 percent that never gets lost. Just

by doing this very simple introspective experiment, he was able to come up with very important aspect of memory that is there are multiple phases in which the memory could be retained. He called those words or those fraction of words that stayed until the duration of the task and little around that time, he called that as immediate memory.

In the present day we call it as working memory. The definition is those memories or those details which we are able to retrieve and stays there with us until the duration of the task. Once you are out of the stars then it is harder for you to retrieve them. The second phase called as short term memory and these are the in between guys. So, these fractions of words were staying with him after the task, but not like the other guys which state forever. They would eventually retain a decline, but they were able he was able to retain them for some time some duration which is larger than the task duration itself.

Hours to days one would like to say, but that is the short term memory as we know in the modern terminology to and important fraction the long term memory; that is the memories that lasts for months to years. This is the 20 percent fraction that we saw in the graph. Now, this idea or this notion that memories can be classified into three different phases and just by looking at the lifespan of it was phenomenal. But this notion of postulating the nature of memory and going ahead and testing it right that kind of set the tone designing an experiment around learning in memory.

So, how do we design the experiments? If you look at this carefully, if you study this carefully you can think of this whole experiment consisting of multiple kinds of blocks of time, blocks of period or phases of experimentation. The first phase the number 1 phase you can think of as a pre-training phase, second followed by a training phase and then a testing phase.

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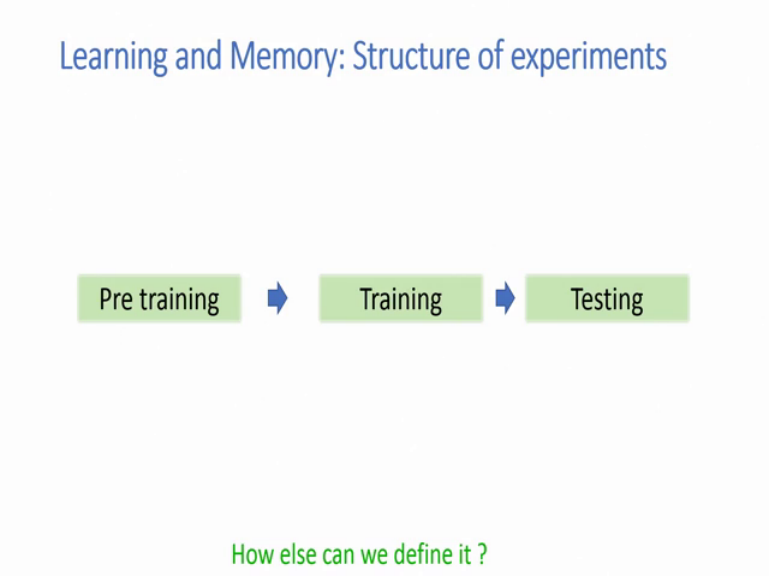

So, the pre-training is the time where you prepare for the experiment. In the sense you need to you need to make ground rules, you need to familiarize yourself about the tasks such as ok, I am going to take this chit out from this and I am going to monotonically read it without any wise modulation. So, that takes some practice. So, that you do not leave any other clues to your brain that can aid in memory right. So, you are testing a particular aspect of memory and you want to just test that and nothing else. So, like that today even today when we are doing these experiments in animals this notion exists.

So, where we need to make sure these are the animals are familiarized with the tasks, we do that through a process called habituation and of the animals. And, it its also has to do with the fact that when you are testing and when you are handling the animals, the animal should not freak out just because some external I mean some other organism is actually trying to lift it up. And, it does not you do not want them to be anxious.

So, you handle them you habituate them and then the idea here is to train them in a task. So, that you can later on go ahead and test it, that is the notion of pre-training, training and testing. So, the pre-training allows you to set the ground rules for the task that you wish the animals going to press, you use the animal is trained for or learn the animal is able to learn. Say for example, you are going to make the animal learn a task where the food as a reward. So, then one of the important thing is to make sure that the animal is wanting to eat the food.

So, how do you do that is you make sure that the animal is on a clock for the food. So, the ratio schedule the is put on for the animal normally in a lab setting the animals that eat the food at will. So, there is no particular schedule. So now, you can impose a schedule such that they are expecting they are expected to eat the food in a defined time period; if they do not eat it then they will not get it. So, as a result there is an a value for the food that is given during the experimentation. So, all these things are done during the pre-training phase. The training phase is really the phase where you are presenting a task in which the animal learns to perform it.

Once during this process you are you can device a metric through which you can measure the performance and you follow the performance. Once a set performance level is reached then you can go ahead and test the animal how well the animal has learned this task. Testing really is about testing the memory of the training that they have, that you have imparted into the animal. And, what they have learned on how well they are actually remembering and the task itself. By analyzing the animal's behavior in these three different phases, one would be able to dissect out the various aspects concerning the learning and memory itself. And, that is if you look at the entire course every single experiment that I will be describing to you and the inferences that I will be drawing, you would be able to generalize into these three different categories, these different blocks.

I may looking at the pre-training period, looking at the training period or maybe I am looking at the entire that the behavior in this entirety ranging from pre-training, training to testing. Let us do that within a very simple example here. So, we know that Hermann Ebbinghaus did his experiments on himself to show that there are three different phases of memory. Today thanks to multitude of experiments done on lab animals, human beings and several other conceptual advances; we know that we do not have to make this definition of these phases; like that short term immediate and long term in a heuristic manner right. He just looked at the curve, the decay curve of the memory retention and then said hey somebody is decaying faster, somebody is little slower, somebody it does not decay at all.

So, let us let there be these three phases, we do not have to do that we can actually more objectively approach this problem and try to ask are there different substrates, are there different ways in which these informations are stored in the brain. If so, can we go ahead and test it and we know they are stored in different ways. I am going to describe an

experiment to demonstrate that they are stored in three different ways. I am going to use this paradigm pre-training, training and testing to actually do accomplish my task. So, how do we do that let us start with the group of animals.

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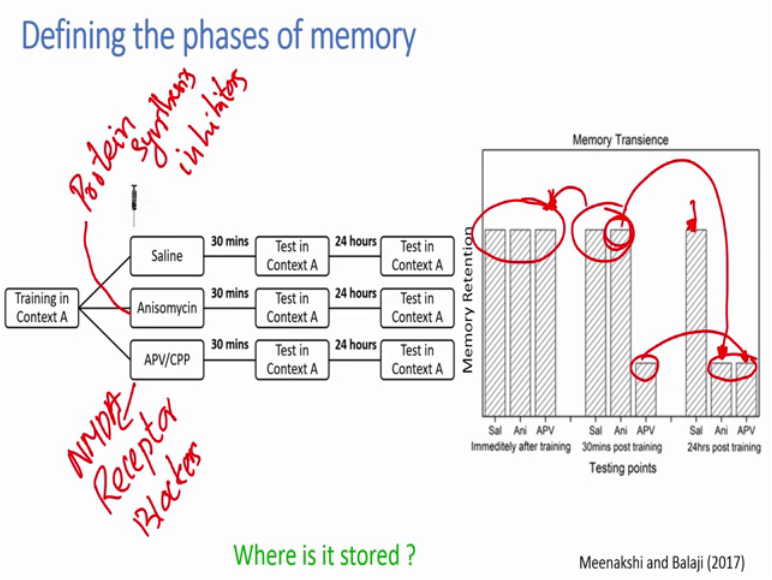

And so, the idea is remember we are going to define the three different phases of memory in a much more, with a much more stronger physical basis alright. So, first what we will do is that we will train these animals in something called as a context ok. So, the idea is that the animal needs to remember the context, we are going to test it. So, there will be different measures of performance and during the training and testing. So, let us not worry about the measures as of it now, but let us look at the notion, let us look at the bigger idea of testing this memory at different points in time or different through different interventions. In this particular case I am going to be doing both, interventions as well as through different points in time.

One of the hypothesis thanks to the research that I talked to you about is that for you to remember for a long period of time, remember the 20 percent fraction that I was talking the equivalent of that; our researchers research show that protein synthesis dino protein synthesis is essential. If you block it you will I mean is essentially without that you will not have this long standing memory. So, the immediate task that we would like to do is to let us say somehow we block this protein synthesis, then does the memory not, do we not see this 20 percent, that we not see this long standing memory ok. So, that is the question

that we are going to ask. So, to address that let us look back at the design. So, first group that you would like to do is that ok, hey look I am going to try in this animal to remember a context.

And, then what I am going to do is that I am going to infuse, I am going to intervene with an infusion of a drug called anisomycin that is this. So, this drug is known to stop the protein synthesis, I am going to infuse this drug right after the training ok. And then test in about 30 minutes ok. So, we have trained hopefully the memory is formed and we are going to infuse this drug in 30 minutes, we are going to test it. Just by looking at the performance here, we know if the memory is formed and if it is formed how well it is formed. Then we are also going to test it 24 hours later right. Why is that important? This is important because see what we are trying to show is that we are going to test is that protein synthesis is important for retaining the memory for a longer period of time, that is the idea that we are going to test. The way we are going to test status using this notion of training and testing, pre-training is done such that the animals are being handled by the experimenter.

And they had to be injected, the act of injection should not cause any such disturbances such that they get freaked out, they do not express the memory. So, you do not want to conclude because of this you are seeing a deficit in memory. So, you do that by two means: one you really make sure there is a habituation phase where and handling phase where you are training the animal and making sure that they are not freaked out with the experimental. However, for injecting itself injecting the drug itself and doing this on the experiment they you really want to have something called as a control group, wherein you inject everything except the drug.

Because, see the drugs are usually dissolved in a vehicle, it is called saline in this case and you are in injecting that drug plus the vehicle into the animal. So, what you can do now here is that we do not inject the drug, but we just inject the saline alone. So, that would be a very good control. If it is the drug that is actually causing the stoppage of the protein synthesis as a result you are failing to see a memory strengthening over or retention of memory over that period of time. Then this group wherein you do everything exactly the same except for the drug, there is no drug here. You are injecting the saline the vehicle and going forward with exactly the same things that you have done in this group.

Then by comparing the performance of this animal at these different points, they are equivalent time points right, they are equivalent things except for this drug. So, by comparing this performance you can actually conclude what role protein synthesis actually plays. Similarly, so that would work to test at which point in time the memory retention is actually failing it is giving up right. You can also do something else in here just to stress on the point and another experimental group wherein, infuse at drug called APV or CPP these are called as this come under a special class of drugs. So, anisomycin is protein synthesis inhibitors. These are receptor blockers NM, more particularly its a NMDA receptor blockers. Their function is different towards I mean as we go along this course we will understand these functions better. But, we will not right now we do not need to know about what these functions are; all we need to know is these are two different molecules: molecule A anisomycin, molecule B APV.

And there is a third group where we just infuse something on which these two molecules are dissolved. Then what we are going to do is that we are going to test them at two different times 30 minutes and 24 hours later. If you do that what you see is that the memory retention ok, when you measure right after the training they are all equal. So, all the three groups are would perform equal ok. However, if you were to measure them 30 minutes post training, could give a gap take them out and if you do that 30 minutes later; you will see that the APV that this group that the third group will not have, will have an impaired memory. While, the other two or as good as the memory that as will perform as good as when there are performing right after the training.

Of course, when you do it you also want to have three different groups for three different time points that is bit of a detail. So, what you are talking about is that this group of mice on an average would also perform similar to this group of mice that has tested very much close to the training, right after the training. Here is the peak of the experiment which is, if you were to test 24 hours later only the saline group will show the retention of memory. However, the both anisomycin we call it as molecule A and APV the molecule B both those groups or sure no retention of the memory, she did the this guy did not have the memory even at 30 minutes. So, he continues to not have this memory. These group right they were having memory at 30 minutes; however, 24 hours later they do not exhibit any memory retention. Clearly, the drug or the molecule that we infused prevented the animals in forming this long standing memories, that molecule is different

from the molecule that is capable of blocking the formation or the acquisition of the memories themselves.

Because, initially they were having and these guys are not having it and it is nothing to do with the training, you can train I mean you can train them there that is not happen any different way. And, all three seem to be at a normal levels. Now, that is a formal way of dissecting out different phases of memory. Now, can clearly see this involved pre-training phase where, we made sure that the animals are handled and be comfortable and they are not anxious. And, there is a training phase where we are making the animal learn that something has been taught context you in this case and then we are testing in between we are intervening with different drugs.

Now, that kind of phenomena that kind of notion of an experimental design is what I was talking to you about pre-training, training and testing phase defines many of the experiments that we do in our learning and memory field. And, just by using this kind of experimental design we would be able to elucidate lot more informations. Example 1: we were continuously talking about storage of an information that has been acquired, that is been learnt right, that is the resultant of a learning or a training task. First thing that you want to ask is, if something is stored in the brain then can we zero in on where exactly is that being stored.

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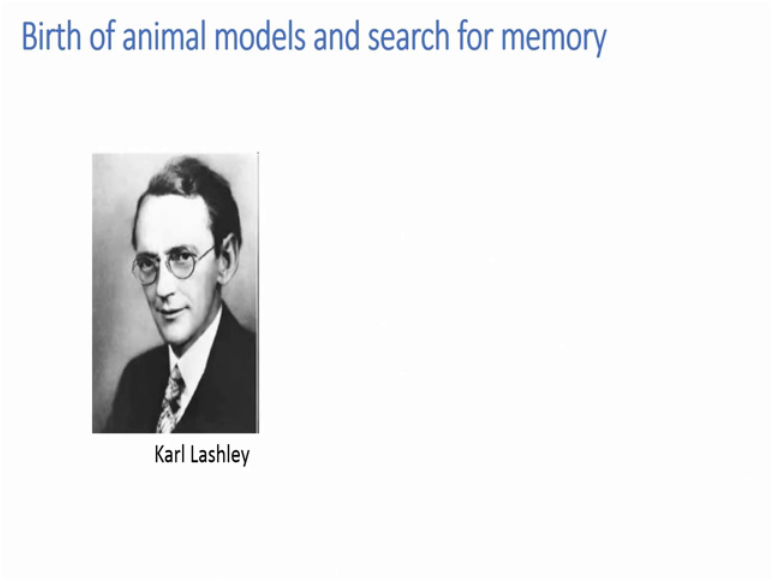

So, Karl Lashley started to ask that such questions. The way he did that is he took rats and then trained them in this task, maze task.

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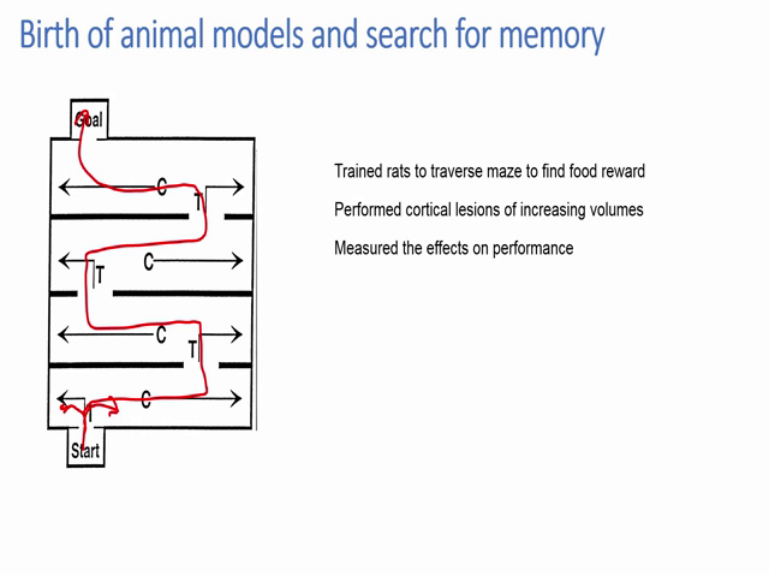

Maze is just a big device of where you are letting the animal go, the animal goes in and then the animal has a choice of making a left or a right turn of which one of them is a correct turn. The correctness is defined by its ability to follow that path, follow a path to a goal box. See a start box, if it makes a right turn it will lead you closer to the goal box while, the left turn will lead it to a blindfold blind spot. So, if you keep on doing that blind then what and then making the correct turns, then in a shorter period of time, I mean without making much of the wrong turns you are you will be able to make the reach the goal.

By measuring how many wrong turns the animal is actually making before reaching the goal, you can actually monitor his performance. His task was now, I am going to take these rats and then train them in this task and measure their performance. Measure their performance as a function of what? I am going to actually perform car lesions cortical lesions. So, he would actually open up the skull and remove a portion of the brain in the rat and the rat survives no issues there and then ask the animal to perform. The idea the here is, if there is a region in the brain and if I am a region in the brain that is storing this information. If I am actually progressively increasing my lesion volume at some point, I am bound to hit that region.

Until, I hit that region the decrement I should see in the performance should not be much. But, once I hit that region there should be a sudden change in the performance, in the performance that I see because just I remove that region, I have removed that memory. Now, the animal should not be able to perform this task, should not have know which is the correct turn and which is the wrong turn; should make as many errors as it used to make during the start of the training. That is a fantastic idea and fantastic notion, but what did he see.

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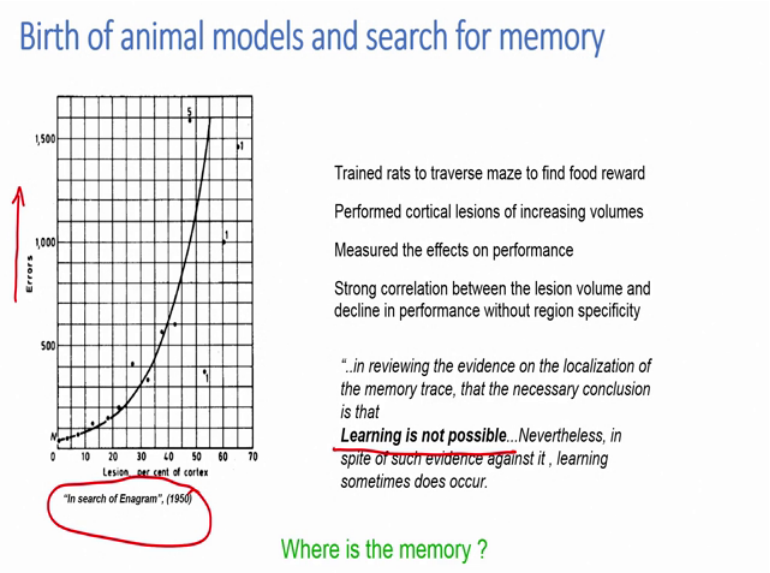

What he saw was there was no such drastic change, granted the progression the decline in performance that we are plotting that he was plotting as a function of the lesion volume right. So, remember please note what he is plotting here is error. So, if the higher is the error lesser is the performance. So, if you see a curve going up the animal is performing lesser and lesser. Here what he is seeing is that as he takes away more and more volume the performance gradually goes up, there is no sudden change.

It is non-linear but, there is no sudden change leading him to conclude no, matter whatever I do it seems as if there is no structural place where, this learning seem to be stored which means learning should not be possible, even though behaviorally I can see the expression of such thing. It was a very depressing note particularly, if I say if I tell you that this whole experiment he did it many more times with lot more different variations. He spent about 30 to 35 years of his time trying to localize the memory. He

summarizes all such all his exploration in this wonderful monograph called in search of Engram and then that is the conclusion he was able to draw. Thankfully, there were many more researchers who were also trying to find or localized memories, though coming from a different angle.

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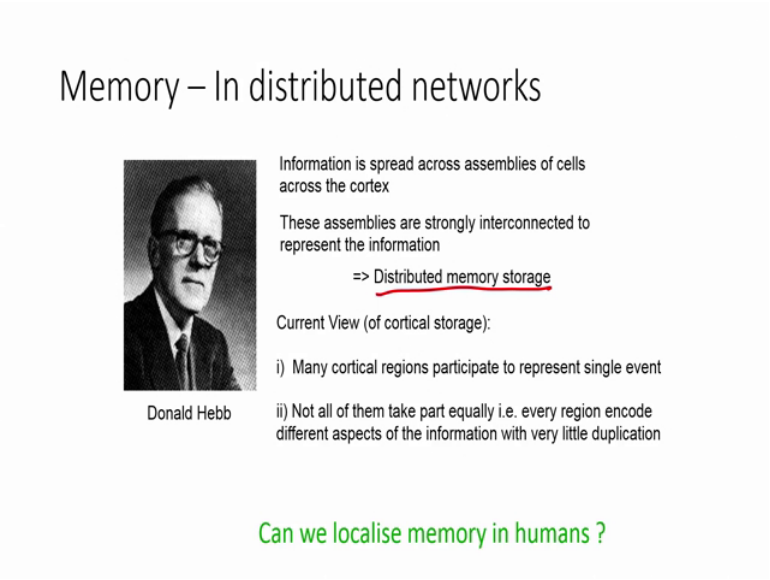

The angle I mean ranges from his own student Donald Hebb. He is known for several other things or but, one of his major contribution is that to explain Karl Lashley's result. What he said was that, hey look this may not look surprising; if you think that memory is not one memory is not stored in one simple place, but it is stored across multiple assemblies. It is like a stored distributed in a distributed manner. So, if you say it is stored in a distributed manner then it so, that is a key word here distributed memory storage. Then, if you are removing a component of it there is sufficient amount of other things are present helping you to actually retrieve the memory. As a result you may not see that all of a sudden change of course, it brings another point how cooperative was these individual informations.

But, the message that he is trying to convey is that there are reasons why you may not see it and it may be fallacious to think that all the memory is stored in one region maybe, that is why Karl Lashley was not able to localize this memories. Currently we do think at least in the cortex the memory is stored in a distributed fashion. And, then more interestingly not all of them take part equally we do know that. And, then if you remove

them you may see the degradation in to various extent. But, the reason why he did not see he saw a monotonic Karl Lashley did not see ranges from various aspects ranging from starting the complexity of the task so on and so forth.

So, that is that besides the point the current view is that it is distributed at least in the cortex. But, if that is so, isn't there I mean if that would say that there is no one you need I mean one unique place that where you can actually go ahead and localize these memories. All along this time there were interesting studies that are happening that involve human patients.

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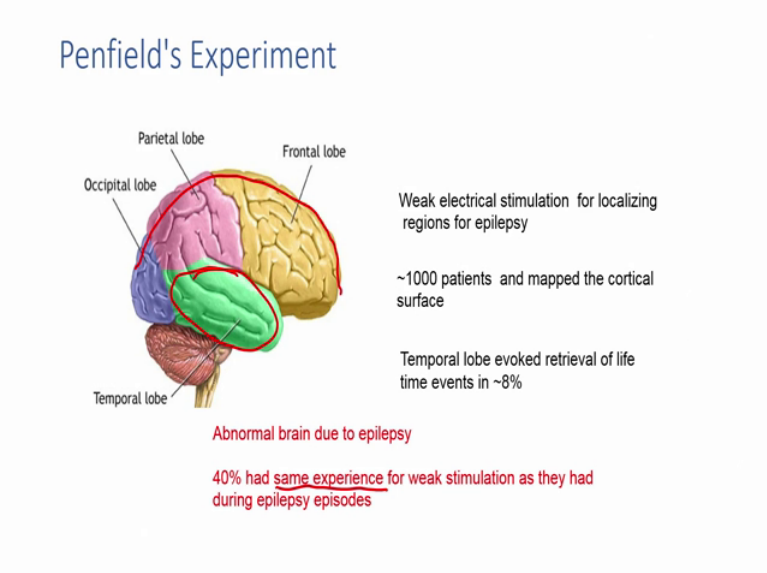

Thanks to Wilder Penfield, a neuro surgeon what he developed was an interesting on the essential a technique for zeroing the non-regions that are causing epilepsy in human patients. So, epilepsy is uncontrolled ceasing behavior. So, what we would do is that in those days to cure this epilepsy when it is going at a debilitating stage is to go ahead and remove that region of the brain even in the humans. So, you cannot go and then remove arbitrary amount of regions without knowing what these things are going to do. So, what you there is a cost associated with it. So, what you will do is that any technique that can zero in that did not help you to zero in on that particular region would be of very great use.

So, what he did Penfield, what Penfield did was to arrive at one such method. He would take to elect he would take an electrode is called a micro stimulating electrodes and he

would do a he will inject a small amount of current, looking at the response of the patient. Idea there is that if you are hitting on the region which is causing epilepsy then you will be able to quickly zero in on that. And, then if there are regions where you do not elicit a response these are kind of a response then you can be leave you can leave them safely there and without disturbing done. In doing so, he found he made some remarkable findings.

One is that he said he was able to map what different what this different regions of this there is of human brain. And, he was able to topographically map what these different regions of the brain do. And, more importantly when he was localizing his micro stimulation on this particular lobe called as medial temporal lobe, he was able to elicit ok. He was able to elicit past lifetime events in many patients, in about 8 a percent of them. Suggesting possibly these are the regions that are storing this memory. So, this is the exact reverse of Karl Lashley's experiments right. He there he was trying to remove a region and seeing the decline decrement in the performance. He is now in here when the Penfield is trying to stimulate a region, activate a region brain region and see what behavioral response you can actually elicit and that is what he saw.

However, the interpretation of these results were hard because, mainly because this is he was working on abnormal brain so that due to epilepsy. So, how do we interpret I mean what do we what do you mean by enacting the lifetime event. And, then to make the curse case worse 40 percent about half of the persons who are able to retrieve whom he was able to help them retrieve the whole time memories, they experienced same they had same experience during the epilepsy episodes too. Leading us to leading people to be say he is really hard to actually say if it is this region that is storing the memory. There is an inclination towards this region, there is a clue towards this region. But, it is not proved, we cannot prove that is the region.

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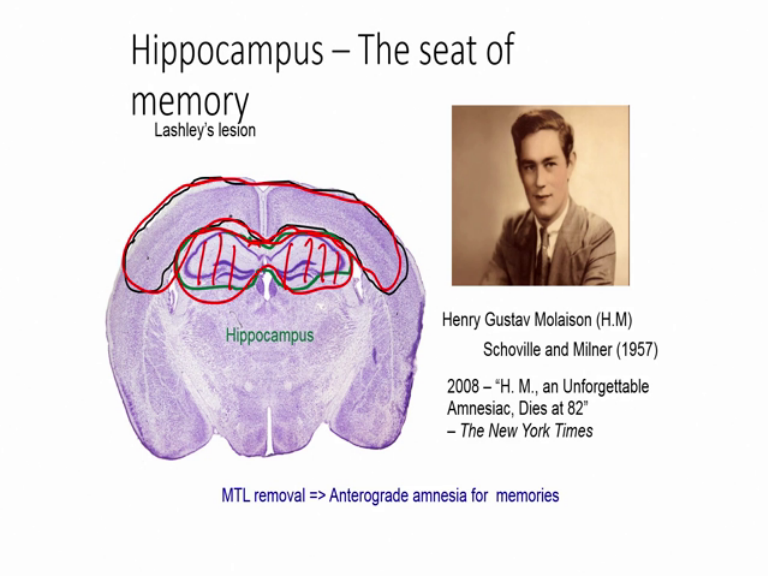

Until, the patient Henry Molaison H.M abbreviated H.M came in. Schoville and Milner Brenda Milner operated on H.M and then for us epilepsy and sure enough after the operation, after the removal of media medial temporal in temporal lobe in H.M his epilepsy was under control. However, during this process they noticed something peculiar. The doctor who was operator who operated on H.M had to introduce himself every day through the entirety of H.M's life after the surgery. H.M would not be able to remember and recognize who this person was, despite the fact the doctor was introducing in himself again and again and again. Even though he would remember his name, his childhood and his family everything else as much as you and I remember. We all have a progressive decline in our memory to some extent right just like Ebbinghaus curve.

When we do lose some amount of memory, but retain a good fraction of them. He was able to retain them there is no problem with that, but his ability to form new memories was severely severely impacted. Giving us the clue that probably what Karl Lashley failed to find we might have found in this human person. And, why could that be the case, why did he fail why did Karl Lashley failed while Schoville and Milner were able to zero in on this region and, then say that there is a memory deficit ability of the person to form new memories is lost, how is possible then. Is it the difference that the rats have different notion of memory, different way of storing the memory while, the humans have it different or something else. To understand that let us look at the anatomy of the brain itself, if you look at the anatomy of the brain.

So, what I am showing here is a section of the brain where, the nostrils of if you place the rat and the mice or the mice brain such that the tail is projecting away from the screen and the nose is projecting out. Then, if you should take a small cross section of the brain that is how it looks and Karl Lashley would go ahead and remove the outermost part of the brain marked here in these black lines. These are the cortical regions and his solutions were on that on those regions. However, the equivalent of the medial temporal lobe in the rat is that the hippocampus.

Now, we know if we were to remove this region in an animal, the animal would exhibit similar loss in memory. So, where his experiment failed is that he was operating on wrong regions for the tasks that he was training the animals in, that is why he was not able to zero in on. However, the findings he had that different amounts of cortical lesions affects the performance in a non-linear manner. But, I mean in a progressive manner still stands and the conclusion that the memories are cortical dependent memories are stored in distributed fashion is true till today.

But the point here this the memories that we are interested in, the memories that one can consciously recollect at well will be lost if you remove hippocampus; just like in H.M. When the remove medial temporal lobe, they made him they H.M developed a class of amnesia called as anterograde amnesia for new memories. With that, I will finish this lecture 1.

Thank you, for listening and I hope to see you in the lecture 2.